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Bismuth: Environmental Pollution and Health Effects

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Abbreviations

| | |
|---------------------|---|
| ARF | acute renal failure |
| BIPP | bismuth iodoform paraffin paste |
| BSS | bismuth subsalicylate |
| BUN | blood urea nitrogen |
| CBS | colloidal bismuth citrate |
| CDDP | cis-diamminedichloroplatinum |
| <i>C. difficile</i> | <i>Clostridium difficile</i> |
| DMPS | 2,3-dimercapto-1-propanesulfonic acid |
| DMSA | dimercaptosuccinic acid |
| ENT surgery | ear, nose and throat surgery |
| EP additive | extreme-pressure additives |
| <i>H. pylori</i> | <i>Helicobacter pylori</i> |
| MIC | minimum inhibitory concentration |
| MT | metallothionein |
| PPI-based | proton pump inhibitor-based |
| RBC | ranitidine bismuth citrate |
| <i>S. aureus</i> | <i>Staphylococcus aureus</i> |
| SARS-CoV | severe acute respiratory syndrome coronavirus |

Introduction

Bismuth was probably unknown to the Greeks and Romans but became familiar during the Middle Ages. It is considered a metal in the periodic table but has more similarity to semimetals. As a relatively rare element in the earth with an estimated natural abundance of 0.2 parts per million, bismuth is always a by-product of the processing of other metal ores such as lead, silver, tin, copper, and zinc. It has been widely used for various purposes. The substitution of lead with bismuth in the manufacturing industry has drawn growing attention recently in terms of resolving environmental problems caused by heavy metal pollution because bismuth shares many characteristics of lead but is much less toxic to living organisms. Nowadays, major applications of bismuth in medicine and health care are related to its high effectiveness in treating a variety of diseases caused by microbial infections and to its potential activities against viruses and tumors. With the development of new therapies and better understanding of the mechanism of action of bismuth, the applications of the metal in health care will be extended further.

Consumption and Distribution of Bismuth in the World

Bismuth is the 69th element in terms of its natural abundance in the earth's crust. The estimation of world's bismuth reserves is usually based on the content of lead resources since bismuth is most often a by-product of lead production; only the Tasna Mine in Bolivia and a mine in China produce bismuth as a major product. Consumption of bismuth has expanded fairly rapidly over the last decade. In 2008, approximately 15 000 tons of refinery bismuth were produced worldwide. Among all the countries, China was the leading producer of refined bismuth with $\approx 80\%$ of the world's total production, followed by Mexico, Belgium and Peru with $\approx 7.8\%$, 5.3% , and 4% , respectively. The estimated reserve of bismuth in the world is shown in [Figure 1](#).

Bismuth in the Manufacturing Industry

In comparison to majority of the other heavy metals, the low toxicity marks bismuth as a kind of 'green' element for the environment. Bismuth compounds and alloys enjoy widespread commercial applications such as in the production of lubricating grease, chemicals, catalysts, shot bullets, cosmetics, fire sprinkler systems, solders, thermoelectric materials, pigments, fishing sinkers, $^{235}\text{U}/^{233}\text{U}$ carriers, medicines, malleable steels, etc.

The semimetallic crystal structure of bismuth along with its other physical-chemical properties such as expansion on solidification, the widest range between melting and boiling points among all metals, and the lowest thermal and heat conductivity make bismuth an ideal substitute for lead analogs in extreme-pressure additives (EP). Substitution of the once widely used lead-based EP additives by bismuth-sulfur additives not only provides a higher lubricant efficacy but also reduces by a half the amount of heavy metal used in extreme-pressure lubricants, in accordance with the new ecological and environmental philosophy of the world. In recent decades, the substitution of lead with bismuth in glass production may lead to potential application for bismuth in the manufacturing of automobile glass, the finest tableware, and art objects, with a purpose of environmental protection. In North America, Bi-Sn has been used to replace lead in shotshells for the hunting of wetland birds. Although the bismuth-containing shotshells cannot be approved as 'nontoxic,' in comparison with the high

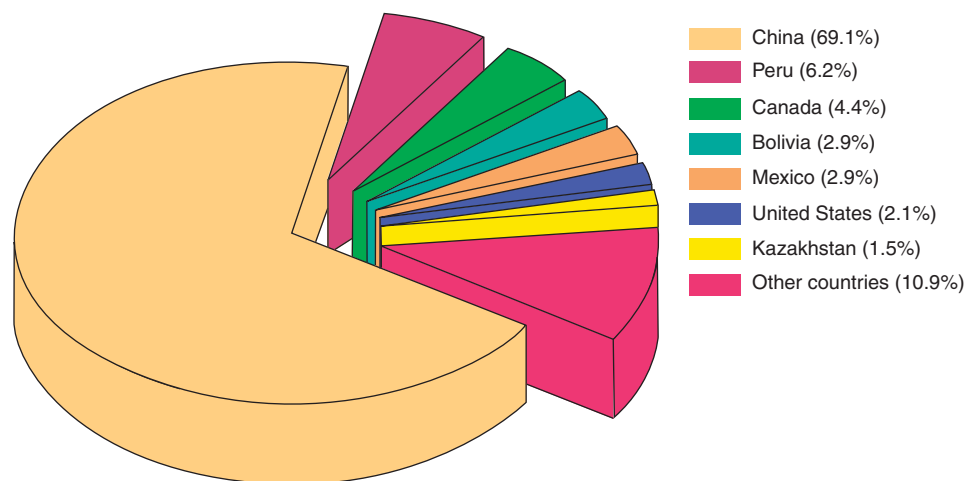


Figure 1 Estimated global bismuth reserve base. Adapted with permission from the *USGS 2009 mineral commodity summary*.

toxicity of lead (e.g., a toxic intake level of 1 mg for a 70 kg human), the high tolerance to bismuth among humans (e.g., a toxic intake level of 15 g for a 70 kg human) renders it a 'relatively' safe substitute for preventing environmental problems caused by lead accumulation. Owing to their satiny luster and low absorption properties, some bismuth compounds such as bismuth oxychloride and bismuth vanadate have also been used in cosmetics including nail polishes, lipsticks, and eye shadows. Recently in Europe, the Restriction of Hazardous Substances Directive (RoHS-2002/95/EC) has stated that lead must be eliminated in the manufacturing of various types of electronic and electrical equipments. This restriction, which has been supported by commercial and research organizations in Japan and North America, will tend to increase the demand for bismuth in industry in future, and will accelerate the replacement process of lead and other heavy metals with bismuth in the manufacturing industry.

Bismuth in Medicine

The use of bismuth as a drug was first reported in 1786 by Louis Odier for the treatment of dyspepsia. Nowadays, based on the gradually comprehended characteristics of this element, many bismuth compounds have been synthesized and developed as new medicines for treatment of many diseases. Currently, many bismuth drugs have been mainly used as antimicrobial and anticancer agents.

Bismuth Compounds as Antimicrobial Agents

Bismuth compounds have been widely used in the treatment of various microbial infections such as syphilis (sodium/potassium bismuth tartrate, bismuth quinine iodide, iodobismutol, bismuth chloride, etc.), colitis

(bismuth subnitrate and bismuth citrate), wound infections (bismuth oxide), quartan malaria (sodium bismuth thioglycolate), dyspepsia (bismuth subsalicylate, bismuth subnitrate, etc.), diarrhea (bismuth subsalicylate, bismuth nitrate, etc.), and peptic ulcers (e.g., colloidal bismuth subcitrate, bismuth subsalicylate, and bismuth subnitrate). Bismuth subsalicylate (BSS, Pepto-Bismol[®]; the Procter & Gamble Company, Cincinnati, Ohio, USA) has been widely used in the United States to treat stomach discomfort and travel diarrhea for decades. Bismuth citrate-based compounds, such as colloidal bismuth subcitrate (CBS, De-Nol[®]; Gist Brocades and Astellas Pharma, Inc. and ranitidine bismuth citrate (RBC, Tritec[®] and Pylorid[®], GlaxoSmithKline plc.), have been used for the treatment of gastrointestinal disorders. The therapeutic efficacy of bismuth citrate-based drugs against the infection of *Helicobacter pylori* (*H. pylori*, an organism that was first discovered in 1983) (Figure 2) may be attributed to the antimicrobial activity of bismuth and the formation of a polymeric 'coating' on ulcer craters, which prevents the erosion of gastric acid (Figure 3). Since ranitidine is an H₂-receptor antagonist that competes with histamine for binding at H₂-receptors that induce the secretion of stomach acid, the use of ranitidine bismuth citrate (RBC) as an antiulcer agent can prove more efficient.

The newly developed bismuth-based triple or quadruple regimens, which combine the bismuth citrate-based drugs with antibiotics such as amoxicillin, tetracycline, clarithromycin, or nitroimidazole, have been often recommended in clinics for treating *H. pylori* infection. Compared to the normally used proton pump inhibitor-based (PPI-based) triple therapies, bismuth-based regimens are more efficient in first-, second-, and third-line *H. pylori* eradication therapies (Table 1). A new drug of bismuth with *D*-polygalacturonic acid, the so-called 'colloidal bismuth pectin,' was approved for clinical use

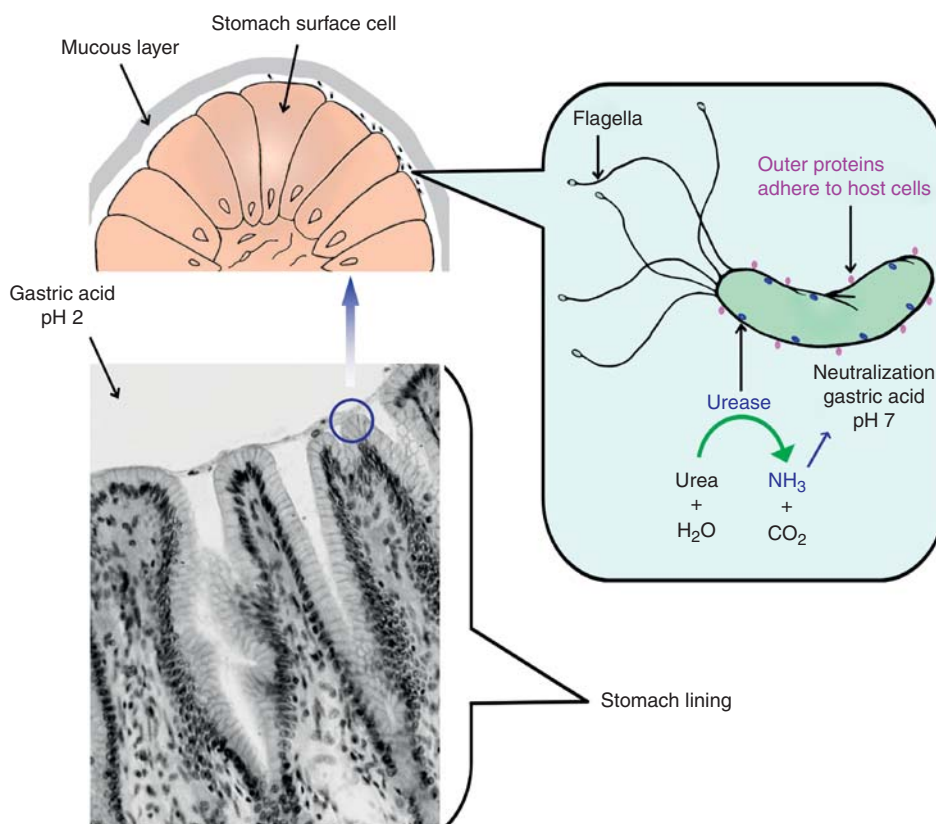


Figure 2 *H. pylori* can burrow through the mucous layer and latch on to stomach cells, where the nickel enzyme urease catalyzes the conversion of urea to ammonia that neutralizes the gastric acid for bacterial survival.

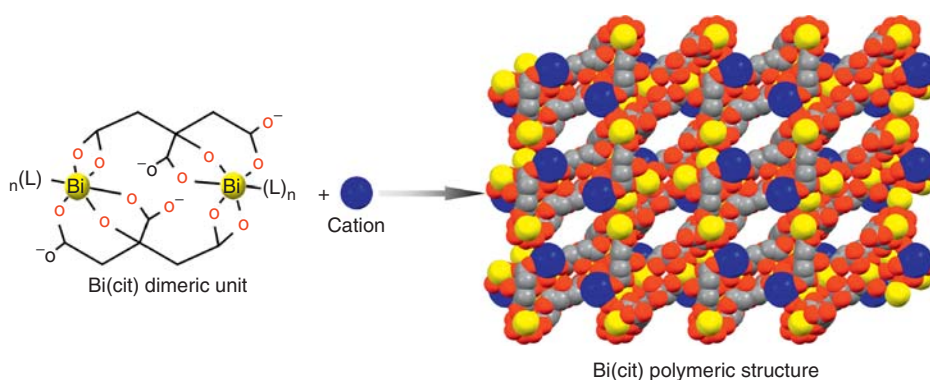


Figure 3 Formation of bismuth citrate ($[\text{Bi}_2(\text{cit})_2]^{2n-}$ or $\text{Bi}(\text{cit})$) polymeric structure by the dimeric unit ($[\text{Bi}_2(\text{cit})_2]^{2-}$). The polymeric framework probably coats on the ulcer craters to prevent the erosion of gastric acid. The negatively charged $[\text{Bi}_2(\text{cit})_2]^{2n-}$ framework is balanced by cations. Color code: Bi, yellow; C, grey; O, red; cation, blue.

in China in the treatment of peptic ulcers and has achieved an effectiveness similar to colloidal bismuth subcitrate.

In addition to the currently used bismuth drugs, newly developed bismuth compounds also exhibit potential antimicrobial activities. It was shown that the antimicrobial activities of bismuth are greatly enhanced when bismuth is combined with thiolate-containing

organic ligands such as 1,3-propanedithiol, dimercaprol, and dithiothreitol. These complexes show antimicrobial activity not only against *H. pylori* but also against some other microorganisms such as *Staphylococcus aureus* and *Clostridium difficile*, with a minimum inhibitory concentration (MIC) at the micromolar level. Although the thiolate ligands can form highly stable complexes with bismuth ions (e.g., a formation constant ($\log K$) of bismuth

Table 1 The efficacy of first-, second-, and third-line *H. pylori* eradication therapies

| Therapy | Regimen | Number treated | Number successful | Success (%) | Bacteriolytic in regimen |
|---------------------|-----------------------------|----------------|-------------------|-------------|---|
| First-line therapy | PPI-based regimens | 364 | 243 | 66.8 | Amoxicillin, nitroimidazole, clarithromycin, erythromycin, and tetracycline |
| | Bi-based regimens | 105 | 100 | 95.2 | Amoxicillin, nitroimidazole, and clarithromycin |
| Second-line therapy | PPI-based regimens | 16 | 6 | 37.5 | Nitroimidazole, amoxicillin, and clarithromycin |
| | Bi-based regimens | 50 | 36 | 72.0 | Nitroimidazole, tetracycline, amoxicillin, and clarithromycin |
| Third-line therapy | Other regimens ^a | 14 | 8 | 57.1 | Omeprazole, rifabutin, and amoxicillin |
| | Bi-based regimens | 6 | 5 | 83.3 | Clarithromycin, tetracycline, and tinidazole |

^aRegimens were chosen from culture and sensitivity test results after the second-line therapy.

Adapted from Beales ILP (2001) Efficacy of *Helicobacter pylori* eradication therapies: A single centre observational study. *BMC Gastroenterology* 1: 7–15, with permission from the BioMed Central.

glutathione complex of 29.6), the thiolate ligands are kinetically labile and can exchange with free thiols on a millisecond time-scale, resulting in a high mobility of bismuth ions inside cells. Owing to this intracellular equilibrium, bismuth ions can be partially released from the drugs and can exert their antimicrobial roles. Since nanotechnology has been extensively explored in recent decades, bismuth-based nanomaterials have also received more attention in pharmaceuticals. For example, bismuth subcarbonate ((BiO)₂CO₃) nanotubes exhibited slightly higher activities against *H. pylori* than the clinically used colloidal bismuth subcitrate under similar conditions, and importantly, bismuth nanotubes could be used as ‘capsules’ in bismuth-based triple or quadruple therapeutic approaches toward the treatment of *H. pylori* infection, or as drug ‘carriers’ for sustained-release of other ingredients in the human body, when used in combination with other drugs in the treatment of other diseases.

Bismuth Compounds as Anticancer Agents

Bismuth compounds were found to exhibit antitumor activities in several cell lines. Bismuth thiolate and oxine complexes exhibited antitumor activities at micromolar concentrations (μM). A water-soluble bismuth cyclen-based compound (Bi-TPC) exhibited an anticancer activity of 100 times more potency than cisplatin (*cis*-diamminedichloroplatinum, CDDP), a widely used anticancer drug, probably *via* interactions with DNA under physiologically relevant conditions.

Recently, it has been shown that radioactive bismuth (²¹²Bi and ²¹³Bi) exhibits promising potential as a novel therapeutic agent for small volume tumors. Both ²¹²Bi and ²¹³Bi have a series of branched decays, resulting in the emission of α-/β-particles. Although the half-life of ²¹²Bi is short (*t*_{1/2} = 1 h), radioactive lead (²¹²Pb,

*t*_{1/2} = 10.6 h) can be used as an *in vivo* generator of ²¹²Bi. With their short-ranged penetration (50–80 μm), bismuth radionuclides can reduce the nonspecific irradiation to normal tissues around the target cells. Furthermore, in order to conduct bismuth to the site of diseases effectively, a chelate ligand can be used together with bismuth radionuclides. In this type of combination treatment, the strong chelate ligand is conjugated to a monoclonal antibody or a fusion protein, a standard treatment for tumors, *via* modification of the ligand to eventually produce a bismuth-radiolabeled ‘complex’. Once the metal radiolabeled ‘complex’ is introduced into the host, it targets specific cell types or sites of diseases and releases the α-particles only at or near the tumor tissues, thereby minimizing damage to the surrounding normal tissues.

Other Potential Medicinal Applications of Bismuth

There have not been reports about antiviral applications of bismuth compounds with the exception of bismuth sodium triglycollamate, historically used to treat warts. Recently, bismuth was discovered to be effective in inhibiting severe acute respiratory syndrome coronavirus (SARS-CoV) with an IC₅₀ less than 1 μM. The potential target of bismuth is the SCV NTPase/helicase, a zinc-containing enzyme that has RNA capping activity and controls the virus reproduction. Binding of bismuth may induce conformational changes in the enzyme, which subsequently affects the helicase RNA/DNA unwinding activity, thereby inhibiting the virus proliferation (Figure 4).

Another potential application of bismuth compounds is in the reduction of side effects of the anticancer drug, cisplatin. Cisplatin and its analogs (carboplatin and

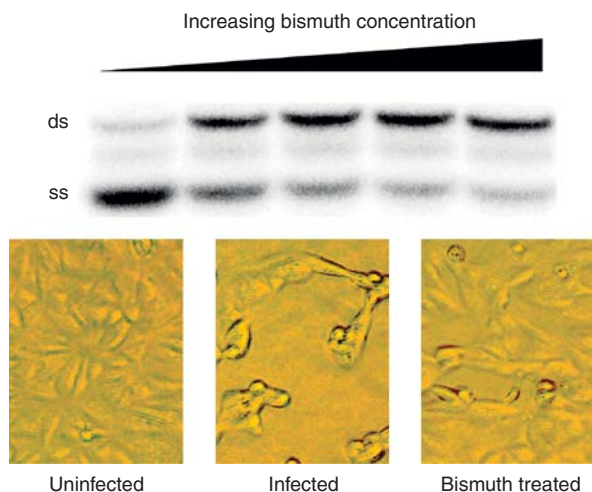


Figure 4 Inhibition of the DNA unwinding activity of SARS helicase by bismuth (top); uninfected cell (bottom left); SARS infected cell (bottom middle); bismuth treated SARS infected cell (bottom right). ds, double-stranded DNA; ss, single-stranded DNA. Adapted from Yang N, Tanner JA, and Zheng BJ, et al. (2007) Bismuth complexes inhibit the SARS coronavirus. *Angewandte Chemie International Edition* 46: 6464–6468, with permission from Wiley-VCH.

oxaliplatin) have been used in clinics worldwide to treat cancers. However, a major obstacle to the more widespread use of cisplatin-based drugs is the persistence of severely toxic side effects. The major dose-limiting effect is nephrotoxicity, including tubular degeneration, loss of brush border, necrosis, and mineralization of the tubular epithelial cells. These renal damages are caused by platinum (Pt). The mechanism of platinum nephrotoxicity may be similar to that of mercury (Hg) and may involve depletion of thiolate groups of the renal tubes. It has been shown that bismuth subnitrate is able to alleviate the side effects of cisplatin, without affecting its anticancer activities. The combination of bismuth subnitrate with citrate can greatly enhance the bismuth protecting virtue due to the increased absorption of bismuth in the kidney, and thereby significantly induce the synthesis of renal metallothionein (MT), a cysteine-rich protein, which plays a key role in protecting the kidney from the effect of heavy metals. *In vivo* experiments showed that pretreatment of bismuth compounds prior to cisplatin therapies can greatly reduce the mice's blood urea nitrogen (BUN) levels, defined as an indicator of renal damage, comparing with the trials without bismuth (Figure 5).

Potential Targets of Bismuth in Biological Systems

Proteins and enzymes have been regarded as potential targets for bismuth in biological systems. Investigations of

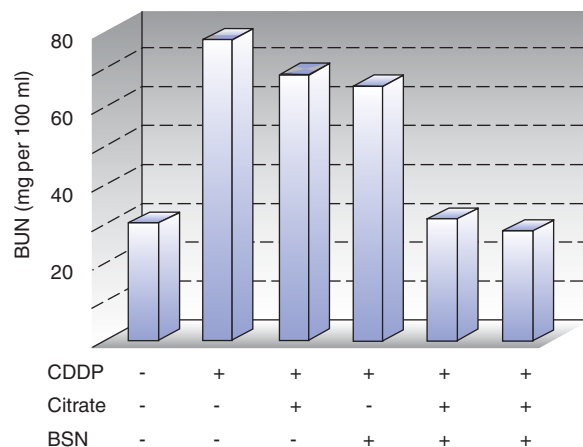


Figure 5 Pretreatment of bismuth subnitrate (BSN) with saline or citrate on renal toxicity of cisplatin (CDDP) in mice. Blood urea nitrogen (BUN) values were measured after the CDDP injection for 5 days. Adapted from Kondo Y, Himeno S, Satoh M, Naganuma A, Nishimura T, Imura N (2004) Citrate enhances the protective effect of orally administered bismuth subnitrate against the nephrotoxicity of *cis*-diamminedichloroplatinum. *Cancer Chemother Pharmacol*. 53: 33–38, with permission from the Springer.

bismuth–protein interactions will not only improve understanding of the mechanism of action of bismuth but will also provide a basis for the design of more effective bismuth agents.

Bismuth was found to be binding to transferrin (an iron transport protein) preferentially to the C-lobe with carbonate (CO_3^{2-}) as an synergistic anion. Transferrin is likely to act as a bismuth transport ‘vehicle,’ as it is only 30% saturated with iron in blood plasma. Importantly, the metal-bound transferrin can be rapidly recognized by the transferrin receptor because of the higher affinity of the receptor to metal-bound transferrin than to its apo-form under extracellular condition (Figure 6). Although human serum albumin is the most abundant protein in serum (0.63 mM) and has been hypothesized to be the target of bismuth in plasma, $\approx 70\%$ bismuth associates to transferrin and the rest to serum albumin, indicating a higher selectivity of bismuth to transferrin. Lactoferrin is another type of major iron-binding protein in the transferrin family, which can also strongly bind to bismuth ions. The bismuth-bound lactoferrin is able to compete with the iron-bound lactoferrin in both the membrane and intracellular, providing another route for bismuth transport. Histidine-rich proteins, such as Hpn and Hpn-like (46.7% and 25% histidine residues, respectively), in *H. pylori* are also potential targets of bismuth ions. Mutagenesis experiments have shown that *H. pylori* with *hpn* gene knock-out are fourfold susceptible to bismuth antiulcer drugs than that of the wild-type, indicating a protective role of Hpn in *H. pylori* responses to bismuth-based therapies.

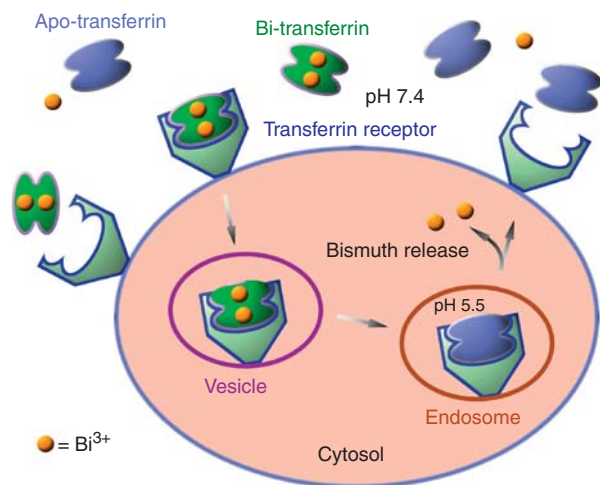


Figure 6 The proposed transport of bismuth (Bi^{3+}) by transferrin mediated endocytosis. Bismuth firstly binds to the apo-transferrin, then the bismuth–transferrin complex is recognized by the transferrin receptor at pH 7.4, the bismuth–transferrin complex is internalized by cells and released in endosomes, followed finally by the release of the metal from the proteins, where the pH is c.5.5.

The interaction of bismuth (Bi^{3+}) with enzymes is related to the high affinity to cysteine residues. For example, bismuth inhibits urease activity probably by blocking the enzyme active site by coordinating to a cysteine residue at the entrance of the active site.

Side Effects of Bismuth

Although bismuth is considered to be nontoxic and as much as 15 g can be tolerated by an adult, the long-term use of bismuth may result in side effects and even toxicity to human subjects. Besides the few cases caused by occupational exposure to bismuth in the manufacturing industry, most of the poisoning incidents occur in the form of accidental or deliberate over-dosage of bismuth drugs. The extent of bismuth toxicity depends on individual cases, that is, the types of bismuth compounds and the amounts absorbed. It is still not clear why only selected individuals develop bismuth toxicity. Patients suffer toxicity at different bismuth levels in blood but the syndrome is rare when bismuth levels are below $50 \mu\text{g l}^{-1}$. Among the bismuth-based regimens, the use of insoluble bismuth compounds such as bismuth oxychloride and bismuth subcarbonate are related to low toxicity, whereas the use of soluble bismuth organic compounds such as bismuth sodium tartrate and tripotassium dicitratobismuthate, or the combined use of bismuth with thiolate-containing ligands, are associated with high toxicity, such as neurotoxicity and nephrotoxicity. This is probably due to the enhanced uptake of soluble bismuth salts in the human body. It has also been

suggested that the oral bismuth drugs need to undergo methylation by intestinal microbes to enable them to be absorbed. Absorbed bismuth will accumulate in the kidneys, lungs, spleen, liver, brain, and muscles, and will be eliminated in urine and feces *via* bile and intestinal secretions. In the clinic, depending on the administration time of bismuth, its toxicity can be roughly divided into acute and chronic exposures. Both exposure doses can cause neurotoxicity, gastrointestinal toxicity, nephrotoxicity, hepatotoxicity, and increased bismuth concentration in blood. In spite of the toxicity, most of these side effects can be alleviated after the discontinuation of bismuth therapies.

Bismuth iodoform paraffin paste (BIPP), which reduces the risk of bacterial infection, renders a deep necrotic wound cavity clean and promotes the development of granulation tissue, and is widely used in oral, maxillofacial, and ENT surgery (ear, nose, and throat surgery) as an antiseptic dressing. However, a few examples of serious adverse effects of BIPP were observed in the clinic when some patients were treated with BIPP. In one case, the patient became acutely confused and the gait became unsteady, indicative of an encephalopathy caused by over-dosage of bismuth. This was confirmed by the observation of a toxic level of bismuth in the patient's serum. Another case involved using BIPP to cover the dura mater in a wound after removal of a large basal cell carcinoma. The patient became confused and then comatose. An encephalopathy was confirmed by the observation of diffuse cerebral edema in a tomographic scan. However, upon removal of the BIPP, the patient recovered, and deteriorated if the pack was applied again. The mechanism of intoxication has not been well understood till now. It was probably caused by the interference of bismuth with the oxidative metabolism of the central nervous system by binding to essential enzymes and reducing cerebral blood flow.

Colloidal bismuth subcitrate (CBS) is widely used to treat peptic ulcer and diarrhea but its toxic effects are rarely reported in the clinic because of the very low amounts of bismuth absorbed from the gastrointestinal tract. There are only few cases on nephrotoxicity after over-dosage of CBS (Table 2). In one case, even the gastric lavage was performed initially, a 2-year-old boy suffered from an acute renal failure (ARF) associated with uremia and oliguria after ingestion of 28 De-Nol tablets (CBS, 8.4 g) for 2 days. After ingestion of CBS for 10 days, bismuth levels in both the blood and urine were 739 and $693 \mu\text{g l}^{-1}$, respectively. With the treatment of peritoneal dialysis, his urine volumes increased and plasma BUN and creatinine levels decreased gradually. After 100 days of admission, the patient recovered and his bismuth level in blood went back to normal.

To cure some serious side effects caused by bismuth over-dosage, some antidotes such as d-penicillamine,

Table 2 Reported adult cases of overdose of colloidal bismuth subcitrate (CBS)

| Sex | Age | Ingested bismuth | Therapy | Outcome | Kidney biopsy or necropsy |
|--------|-----|--|---|-------------------------------------|---------------------------|
| Male | 27 | 100 tablets, 12 g Bi ₂ O ₃ | Hemodialysis, colonic purging, and rehydration | Alive | Absent |
| Male | 76 | 80 tablets, 9.6 g Bi ₂ O ₃ (one-time ingestion dose) | Hemodialysis and colonic purging | Died from perforated duodenal ulcer | Acute tubular necrosis |
| Male | 21 | 39 tablets, 4.68 g Bi ₂ O ₃ | IV crystalloid, furosemide, dopamine, and mannitol | Alive | Acute tubular necrosis |
| Male | 21 | 50–60 tablets, 6–7.2 g Bi ₂ O ₃ | Charcoal, bowel irrigation, chelator (DMPS), and hemodialysis | Alive | Absent |
| Female | 16 | 10–15 tablets, 1.2–1.8 g Bi ₂ O ₃ | Hemodialysis | Alive | Acute Tubular necrosis |
| Male | 2 | 27 tablets, 3.2 g Bi ₂ O ₃ | Gastric lavage, peritoneal dialysis, and IV crystalloid | Alive | Absent |

Adapted from İşlek İ, Uysal S, Gök F, Dündaröz R, and Küçüködük Ş (2001) Reversible nephrotoxicity after overdose of colloidal bismuth subcitrate. *Pediatric Nephrology* 16: 510–514, with permission from the Springer.

2,3-dimercapto-1-propanesulfonic acid (DMPS), dimercaptosuccinic acid (DMSA), and dimercaprol have been tested in animals and limited clinical trials. It was shown that DMPS and DMSA effectively alleviate bismuth poisoning due to their strong chelating ability to bismuth ions.

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